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ART UNIT	**PAPER NUMBER**
1617	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/520,781	URADE ET AL.	
	Examiner	Art Unit	
	Richard A. Houghtling, Ph.D.	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 October 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3-7 and 10* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3-7 and 10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☒ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *See Continuation Sheet*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :11 October 2004 and 17 February 2005.

DETAILED ACTION

1. Claims 1-13 were pending in this application received on October 11, 2004; the examiner acknowledges receipt on April 3, 2006 of a preliminary amendment filed in which the specification and the claim set were amended such that claims 1-2, 8-9 and 11-13 were cancelled. Thus, claims 3-7 and 10 are pending and are examined on their merits, herein.

Foreign Priority

2. Applicants' claim to foreign priority to Japanese application 2003-8230 from January 16, 2003 is acknowledged. Acknowledgment is made of applicant's claim for priority under 35 U.S.C. 119(a)-(d) based upon two applications filed in Japan on July 12, 2002 and January 16, 2003.

Information Disclosure Statements

3. Receipt of two information disclosure statements filed by applicants on October 11, 2004 and February 17, 2005 is acknowledged; examiner entered the disclosures into the record and references were considered.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 3-7 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for treating brain injury using a prostaglandin D receptor antagonist, does not reasonably provide enablement for the prevention of brain injury. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The instant claim is drawn to a method for treatment or **prevention** of brain injury. The instant specification fails to provide information that would allow the skilled artisan to practice the instant invention for prevention of brain injury. Attention is directed to *In re Wands,* 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman,* 230 USPQ 546 (BdAPIs 1986) at 547 the court recited eight factors:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;

(F) The amount of direction provided by the inventor;

(G) The existence of working examples; and

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

Nature of the invention: The instant invention pertains to a method for treating or preventing brain injury.

State of the prior art: The state of the art for a method for the treatment of brain injury in a patient is reasonably well established in the prior art, however, a method for preventing brain injury, which must be completely, totally, absolutely, or permanently prevented is not known and thus not credible on its face.

Relative skill of those in the art: The relative skill of those in the art is high, typically requiring an advanced professional degree.

Predictability or lack thereof in the art: The skilled artisan would view that the method for treatment of brain injury is relatively predictable; however, in order to prevent brain injury totally, absolutely, or permanently prevent its occurrence, as highly unpredictable and not credible.

Amount of guidance provided by the inventor and existence of working examples: In the instant case, 9 working examples are provided in the specification and 27 Figures

are included of which 6 (Figures 16, 20 and 24-27) are directly applicable to the PGD_2 antagonist. Review of the examples and data provided corresponding to the claimed method of administering a prostaglandin D_2 receptor antagonist for prevention of brain injury would require demonstration that administration of the PGD antagonist prior to brain injury had the desired effect to completely, absolutely and totally prevent the brain injury response from occurring.

Although Applicant convincingly demonstrates that brain injury results in increased plasma exudate in the brain parenchyma *via* a time-dependent manner and results in increased infiltration of inflammatory cells, Applicant fails to demonstrate that DP-receptors are critical for either of these responses to brain injury. For example, Applicant shows that mice-deficient in DP receptors by genetic knockout have reduced plasma exudate than wild-type controls, but still, a significant amount of dye leakage is measured (see Figure 26). Furthermore, pretreatment of mice with DP receptor antagonists BW-A868C or ramatroban or pinagladin fail to completely, or totally eliminate all dye leakage (see Figures 24 and 27) or eliminate inflammatory cell infiltration into the injury site as shown in Figures 16 or 25.
Together these data suggest a role for the DP receptor in some aspects of plasma exudation in sites of brain injury and inflammatory cell infiltration, but do not convincingly demonstrate that DP receptor antagonists could prevent brain injury. Thus, none of the working examples provided teaches a skilled artisan how to prevent brain injury from occurring. Note that lack of a working example, is a critical factor to be

considered, especially in a case involving an unpredictable and undeveloped art. See MPEP §2164.

Genetech, 108 F.3d at 1366, states "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague limitations of general ideas that may or may not be workable.

Therefore, in view of the *Wands* factors, e.g., the lack of direction or guidance provided, absence of working examples, and the lack of predictability of the art as discussed above, to practice the claimed invention herein, an artisan would have to engage in *undue experimentation* to test whether prostaglandin D antagonists could in fact prevent brain injury. To do so, an artisan would have to identify every possible marker of brain inflammation, type of injury method, as well as, conduct pharmacological testing to determine whether prophylactic administration of the PGD antagonist could prevent changes in any of the brain injury markers identified. Finally, an artisan would be required to assess any and all mechanisms by which brain injury may occur and verify that the claimed invention does, in fact prevent brain injury to such an extent that it totally, absolutely, or permanently prevent any and all evidence of an inflammatory response to tissue injury following a traumatic insult, and have to do so with no assurance of success.

5. Claims 3-7 and 10 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for treating brain injury

administering some species of prostaglandin D receptor antagonists, does not reasonably provide enablement for the entire genus of prostaglandin D receptor antagonists. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The instant claims are drawn to a method for treatment of brain injury administering prostaglandin D receptor antagonists. The instant specification fails to provide information that would allow the skilled artisan to practice the instant invention for treatment of brain injury using all prostaglandin D receptor antagonists. Attention is directed to *In re Wands,* 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman,* 230 USPQ 546 (BdAPIs 1986) at 547 the court recited eight factors:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

Nature of the invention: The instant invention pertains to methods for treating brain injury by administering an effective amount of a prostaglandin D receptor antagonist. The invention requires that one of skill be able to make every prostaglandin D receptor antagonist within the genus of such antagonists without empirical, undue and unpredictable trial and error experimentation; i.e., the skilled artisan must be able to recognize what structural features confer the antagonist properties of the prostaglandin D receptors and create another antagonist with the same desired characteristic. It is noted that the ability to "identify" an antagonist with the desired property to inhibit prostaglandin D receptors is not equivalent to the ability to make and use a prostaglandin D receptor antagonist based on the above principle.

Scope of the invention: The scope of the invention is very broad, encompassing all antagonists from the genus corresponding to the prostaglandin D_2 receptors, which includes both DP-type and CRTH2-type receptors. However, there is only description of a few specific antagonists provided, and there is no description of CRTH2-type receptor antagonists. As such the skilled artisan cannot make the broad scope of the claimed Prostaglandin D_2 receptor antagonists.

State of the prior art: The state of the art with regard to prostaglandin D receptor antagonists administered as treatment for brain injury is poorly developed. No prior art exists specifically describing administration of such antagonists as a therapeutic modality for brain injury in humans.

Relative skill of those in the art: The relative skill of those in the art is high, typically requiring an advanced professional degree.

Predictability or lack thereof in the art: The skilled artisan would view that the method for treatment of brain injury by administering prostaglandin D receptor antagonists as being unpredictable due to lack of prior art. The state of the prior art itself in regard to the localization or distribution of prostaglandin D receptors in human tissues is a topic of much debate. Initial findings suggested PGD receptor localization limited to the retina and the small intestine; yet, other studies suggested PGD receptor expression on vascular smooth muscle cells as well as localization on T-helper 2 cells. At the time of applicant's invention, the field of prostaglandin D receptor localization and pharmacological development of these receptors was in its infancy of development. As such, the teachings required by applicant to make and use the entire genus of prostaglandin D receptor antagonists is great, because of the variability found in the prior art with regard to receptor affinities and ligand binding specificities of and antagonists for the prostaglandin D receptors—DP-type and CRTH2-type of receptors. Applicants do teach antagonists of DP receptors, yet fail to describe whether these antagonists also have equivalent effects on the CRTH2 receptors and how these receptors are involved in reducing the effects of brain injury. Thus without specific teachings by applicant that provide the necessary examples and show the reproducibility of such findings with CRTH2 receptors and PGD antagonists, it must be

considered unpredictable as to which PGD receptors are responsible for the effects that applicants regard as their invention.

Amount of guidance provided by the inventor and existence of working examples: In the instant case, 9 working examples are provided in the specification and 27 Figures are included of which 6 (Figures 16, 20 and 24-27) are directly applicable to the PGD_2 antagonist. Review of the examples and data provided corresponding to the claimed method of administering a prostaglandin D_2 receptor antagonist for treatment of brain injury include the DP-receptor antagonists BW-A868C, pinagladin, and ramatroban; however, these examples do not specifically include any indication as to the effects that would be attributable to the CRTH2 receptors and thus to the genus of prostaglandin D receptor antagonists.

Although Applicant convincingly demonstrates that brain injury results in increased plasma exudate in the brain parenchyma *via* a time-dependent manner and results in increased infiltration of inflammatory cells, Applicant fails to demonstrate that DP-receptors are critical for either of these responses to brain injury. For example, Applicant shows that mice-deficient in DP receptors by genetic knockout have reduced plasma exudate than wild-type controls, but still, a significant amount of dye leakage is measured (see Figure 26). Furthermore, pretreatment of mice with DP receptor antagonists BW-A868C or ramatroban or pinagladin fail to completely, or totally eliminate all dye leakage (see Figures 24 and 27) or eliminate inflammatory cell

infiltration into the injury site as shown in Figures 16 or 25. Together these data suggest a role for the DP receptor in some aspects of plasma exudation in sites of brain injury and inflammatory cell infiltration, but do not convincingly demonstrate that all types of prostaglandin D receptors and hence, all prostaglandin D receptor antagonists could treat brain injury. Thus, none of the working examples provided teaches a skilled artisan how to treat brain injury via blockade of CRTH2 receptors. Note that lack of a working example, is a critical factor to be considered, especially in a case involving an unpredictable and undeveloped art. See MPEP §2164.

Genetech, 108 F.3d at 1366, states "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague limitations of general ideas that may or may not be workable.

Therefore, in view of the *Wands* factors, e.g., the lack of direction or guidance provided, absence of working examples, and the lack of predictability of the art as discussed above, to practice the claimed invention herein, an artisan would have to engage in *undue experimentation* to test whether administration of each and every species of the entire genus of prostaglandin D receptor antagonists could in fact be administered and treat brain injury. To do so, an artisan would have to identify every possible marker of brain inflammation, type of injury method, as well as, conduct pharmacological testing to determine whether prophylactic or acute administration of each and every PGD antagonist could in fact treat patients suffering from brain injury by analyzing each of the markers identified. Finally, an artisan would be required to

assess any and all mechanisms by which brain injury may occur and verify that the claimed invention does, in fact provide treatment for brain injury, including evidence of an inflammatory response to tissue injury following a traumatic insult, and have to do so with no assurance of success.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

7. Claims 3-7 and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tsuri et al. (1997), further in view of Wong (2000).

Applicant's invention is drawn to a method for treatment or prevention of a brain injury which comprises administering an effective amount of an antagonist for prostaglandin D receptor to a patient in need thereof (claim 3); wherein the antagonist is BW-A868C, ramatroban, S-5751 or pinagladin (claim 4); or prostaglandin receptor antagonists represented by formula I (claim 5), formula IA (claim 6) or formula IA-a (claim 7). Claim 10 is a second independent claim, similar to claim 3 but of a narrower scope as it is limited to a method for treatment and does not include prevention.

Applicant defines the term, "brain injury," to include traumatic accidental injuries to the head, as well as, cerebrovascular disorders (i.e., cerebral infarction and cerebral bleeding), and neuronal degenerative diseases. Furthermore, applicant defines the term, "treatment or prevention of brain injury," to include treatment or prevention of brain contusion, brain edema, cerebral infarction, cerebral bleeding, ischemic brain diseases, Alzheimer's disease, multiple sclerosis and demyelination diseases (Specification, p.3 lines 15-24).

Tsuri et al. teach the (ZS)-7-[1R,2R,3S,5S)-2-(5-hydroxybenzo[b]tiophen-3-ylcarbonylamino)-10-norpinan-3-yl]hept-5-enoic acid via modification of compound 14 using R-group 19 (see p. 3505); also taught is (ZS)-7-[1R,2R,3S,5S)-2-(5-benzo[b]tiophen-3-ylcarbonylamino)-10-norpinan-3-yl]hept-5-enoic acid via modification of compound 14 using R-group 18 (see p. 3505).

Testing of these compounds using an *in vivo* rhinitis model showed 78% inhibition of intranasal pressure induced by antigen challenge in guinea pigs (see p. 3505, Table 2, compounds 16, 19 and 20). Administration of DP antagonists reduced intranasal pressure largely by inhibiting vascular permeability (edema) and prevention of airway resistance (see p. 3506, Table 3) as well as reduced the number of immune cell (eosinophil) infiltrates (p. 3506, col.1, lines 35-44). Thus, these data show that PGD_2 antagonists have promise for alleviating allergic diseases by reducing inflammation (edema, eosinophil infiltration and bronchial smooth muscle relaxation).

Tsuri et al. does not teach use of PGD_2 antagonists as a method for treatment or prevention of brain injury.

Wong teaches the pathophysiology associated with primary brain injury. Following brain injury, a primary inflammatory response is triggered which increases vascular permeability and vasodilation that leads to vasogenic edema, cerebral ischemia and impaired autoregulation which leads into a cyclical pattern of reduced ATP and increased lactic acidosis, increased ion and water influx into cells, resulting in cytotoxic edema that exacerbates the existing cerebral ischemia resulting in secondary brain injury (see p. 18, col. 3; p. 19, col. 1-2; and p.20, Figure 1).

Wong does not teach use of PGD_2 antagonists for use in a method for treatment or prevention of brain injury.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to employ PGD_2 receptor antagonists for treatment of brain injury because of the anti-inflammatory properties of these drugs disclosed in the prior art.

One having ordinary skill in the art would have been motivated to employ a Prostaglandin D receptor antagonist such as those taught by Tsuri et al. which are shown to have a high affinity for DP-receptors (see Table I, compounds 18 and 19) and reduce the inflammation associated with rhinitis (see Table 2, compound 19). Specifically, instantly claimed compounds pinagladin ((ZS)-7-[(1R,2R,3S,5S)-2-(5-benzo[b]tiophen-3-ylcarbonylamino)-10-norpinan-3-yl]hept-5-enoic acid) and S-5751 ((ZS)-7-[(1R,2R,3S,5S)-2-(5-hydroxybenzo[b]tiophen-3-ylcarbonylamino)-10-norpinan-3-yl]hept-5-enoic acid are each taught by Tsuri et al. Tsuri et al. teaches synthesis of applicants' claimed compounds using Scheme 3 (p. 3505, col. 3) by modification of compound 14 and R-groups shown for compound 18 or compound 19, which correspond to the instantly claimed compounds pinagladin or S-5751 (claim 4), respectively. Additionally, the structures taught by Tsuri et al. further represent compounds from instant claims 5 or 6, when X = H, and R = H (pinagladin) or R= OH in the 5th position (S-5751)). Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to employ the Prostaglandin D receptor antagonists taught by Tsuri et al. in a method to treat a head injury in a patient in order to reduce the possibility of inflammation-induced secondary brain

damage resulting from vasogenic and cerebral cytotoxic edema taught by Wong with the end result being that of applicant's claimed invention (claims 3-6 and 10).

Finally, compounds 18-22 (Scheme 3, see p. 3505) taught by Tsuri et al. teach similar compounds to the prostaglandin D receptor antagonist structure I-Aa as in the instant claim 7 except for the stereochemistry. The difference in stereochemistry is an obvious variation as Tsuri et al. teaches similar stereochemical substitutions for the other compounds found in Schemes 1 and 2, and thus it would have been obvious to make similar substitutions in the compounds made using Scheme 3. In lieu of a showing of unexpected results, one of ordinary skill in the art at the time of the invention would have had a reasonable chance of success to make and use this chemical structure using routine substitutions as are taught by Tsuri et al.

Conclusion

No claims are allowed. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Richard A. Houghtling whose telephone number is (571) 272-9334. The examiner may normally be reached Mon-Thurs 8:30 am - 5:00 pm and alternate Fridays 8:30 am - 12:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan may be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-

273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Richard A. Houghtling, Ph.D.

SREENI PADMANABHAN
SUPERVISORY PATENT EXAM.